

# Notice of Allowability

Application No.

09/214,453

Examiner

Kathleen M Kerr

Applicant(s)

LEADLAY ET AL.

Art Unit

1652

## -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to 7/22/04.
2. ☒ The allowed claim(s) is/are 71-98.
3. ☒ The drawings filed on 05 January 1999 and 24 December 2003 are accepted by the Examiner.
4. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
  - a) ☒ All    b) ☐ Some\*    c) ☐ None    of the:
    1. ☐ Certified copies of the priority documents have been received.
    2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
    3. ☒ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\* Certified copies not received: \_\_\_\_\_.


Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.

**THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
  6. ☐ CORRECTED DRAWINGS ( as "replacement sheets") must be submitted.
    - (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review ( PTO-948) attached
      - 1) ☐ hereto or 2) ☐ to Paper No./Mail Date \_\_\_\_\_.
    - (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date \_\_\_\_\_.
- Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

### Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO-1449 or PTO/SB/08),  
Paper No./Mail Date 11/25/02
4. ☐ Examiner's Comment Regarding Requirement for Deposit  
of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☒ Interview Summary (PTO-413),  
Paper No./Mail Date 9/13/04.
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other \_\_\_\_\_.

  
Kathleen M Kerr  
Primary Examiner  
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## **DETAILED ACTION**

### ***Application Status***

1. In response to the previous Office action, an Advisory action (mailed on August 12, 2004), Applicants telephoned the Examiner to propose claim amendments to bring the application into condition for allowance on September 15, 2004. In view of the proposed amendment, the Examiner agreed to enter the after-final amendment filed on July 14, 2004 at this time. Said amendment amended the specification and the claims; in the claims, Applicant cancelled Claims 1, 2, 52-55, 57, 60, and 67-69 and amended Claims 25, 27, 31, 32, 35-37, 44, 47, 50-51, 56, 61-64, and 70. Thus, prior to the Examiner amendment set forth below, Claims 25, 27, 31-37, 39, 44, 47-51, 56, 58, 61-66, and 70 were pending as filed by Applicant.

### ***Priority***

2. As previously noted, the instant application is granted the benefit of priority for the International Application No. PCT/GB97/01819 filed on July 4, 1997 which claims benefit of (1) U.S. Provisional Application No. 60/024,188 filed on August 19, 1996, (2) Great Britain foreign application 9614189.0 filed on July 5, 1996, and (3) Great Britain foreign application 971062.3 filed on May 28, 1997.

### ***Information Disclosure Statement***

3. The information disclosure statement filed on November 25, 2002 has been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

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***Drawings***

4. As previously noted, amended Figures 2b-19, 27, and 29-32 have been filed; new Figure 33, as taken from page 89 of the specification, has also been filed. Said drawings have been approved by the Draftsman and are entered as formal drawings in combination with Figures 1, 2a, 20-26, and 28 of those originally filed.

***Withdrawn - Objections to the Specification***

5. Previous objection to the specification for a large gap on page 94 of the specification as originally filed is withdrawn by virtue of Applicant's amendment.

***Withdrawn - Claim Rejections - 35 U.S.C. § 112, second paragraph***

6. Previous rejection of Claim 54 under 35 U.S.C. § 112, second paragraph, as being indefinite is withdrawn by virtue of Applicant's cancellation of said claim.

7. Previous rejection of Claim 61 under 35 U.S.C. § 112, second paragraph, as being indefinite is withdrawn by virtue of the Examiner's amendment, authorized by Applicant's representative as noted below, canceling said claim.

8. Previous rejection of Claim 25 under 35 U.S.C. § 112, second paragraph, as being indefinite for the antecedent basis of "said loading module" is withdrawn by virtue of Applicant's amendment clarifying said basis.

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9. Previous rejection of Claims 25, 27, 31-37, 39, 44, 47-58, and 60-70 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term “functional polyketide synthase” is withdrawn by virtue of Applicant’s amendment removing said term from the claims.
10. Previous rejection of Claim 63 under 35 U.S.C. § 112, second paragraph, as being indefinite for the clarity of items (a) and (b) is withdrawn by virtue of Applicant’s amendment.
11. Previous rejection of Claims 64-65 under 35 U.S.C. § 112, second paragraph, as being indefinite for the option in item (a) using *Streptomyces coelicolor* as a host cell is withdrawn by virtue of Applicant’s amendment.
12. Previous rejection of Claim 70 under 35 U.S.C. § 112, second paragraph, as being indefinite for the antecedent basis of the synthase in the preamble is withdrawn by virtue of Applicant’s amendment.

***Withdrawn - Claim Rejections - 35 U.S.C. § 112, first paragraph***

13. Previous rejection of Claims 62 and 63 under 35 U.S.C. § 112, first paragraph, new matter, is withdrawn by virtue of the Examiner’s amendment, authorized by Applicant’s representative as noted below, canceling Claim 62; the inclusion of Claim 63 had been in error in the previous Office action.
14. Previous rejection of Claims 69 and 70 under 35 U.S.C. § 112, first paragraph, new matter, is withdrawn by virtue of Applicant’s amendment and/or cancellation of said claims.

***Withdrawn - Claim Rejections - 35 U.S.C. § 102***

15. Previous rejection of Claim 1 under 35 U.S.C. § 102(e) as being anticipated by Khosla *et al.* (USPN 5,962,290) is withdrawn by virtue of Applicant's cancellation of said claim.

16. Previous rejection of Claims 31-37, 39, 47-49, 55-58, 60, 61, and 64-67 under 35 U.S.C. § 102(e) as being anticipated by Khosla *et al.* (USPN 5,962,290) is withdrawn by virtue of Applicant's amendment.

***Withdrawn - Claim Rejections - 35 U.S.C. § 103***

17. Previous rejection of Claims 2, 25, 44, and 68 under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* (USPN 5,962,290) in view of MacNeil *et al.* is withdrawn by virtue of Applicant's amendment.

18. Previous rejection of Claim 27 under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* (USPN 5,962,290) in view of MacNeil *et al.* and in view of Kao *et al.* is withdrawn by virtue of Applicant's amendment.

19. Previous rejection of Claims 51 and 52 under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* (USPN 5,962,290) in view of MacNeil *et al.* and in view of Cox *et al.* (USPN 5,190,871) is withdrawn by virtue of Applicant's amendment.

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***Summary of All Previously Pending Objections/Rejections***

20. All previously pending objections/rejection are withdrawn, as noted above, by virtue of Applicant's amendment and/or the Examiner's amendment below authorized by Applicant's representative as noted.

**EXAMINER'S AMENDMENT**

21. An extension of time under 37 C.F.R. § 1.136(a) is required in order to make an examiner's amendment which places this application in condition for allowance. During a telephone conversation conducted on October 15, 2004, Patrick Hagan requested an extension of time for ONE MONTH(S) and authorized the Director to charge Deposit Account No. 04-1406 the required fee of \$110 for this extension and authorized the following examiner's amendment. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 C.F.R. § 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

***Amendments to the Claims***

22. The claims have been amended as follows:

- a) Delete Claims 25, 27, 31-37, 39, 44, 47-51, 56, 58, 61-66, and 70 (all previously pending claims).
- b) Insert the following new claims, which are representative of all the above previously pending claims.

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---71. A polynucleotide comprising an open reading frame encoding a hybrid polyketide synthase (PKS) that produces a polyketide, said open reading frame comprising:

- (a) a first nucleic acid portion encoding a loading module and adjacent ketosynthase (KS) domain of a first Type I PKS; and
- (b) a second nucleic acid portion encoding a partial extension module of a second Type I PKS, wherein said partial extension module is an extension module which lacks the first KS domain,

whereby said polynucleotide encodes a hybrid PKS that comprises a loading module adjacent to a hybrid extension module.

72. A vector comprising the polynucleotide of Claim 71.

73. A microorganism transformed with the polynucleotide of Claim 71.

74. The transformed microorganism of Claim 73, wherein said transformed microorganism is able to express the hybrid PKS encoded by the polynucleotide.

75. A microorganism, which expresses a PKS in its untransformed state, wherein said microorganism is transformed with the polynucleotide of Claim 71 and is able to express the hybrid PKS encoded by the polynucleotide.

76. A plasmid comprising the polynucleotide of Claim 71.

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77. The plasmid of Claim 76, wherein said plasmid is adapted to integrate into a specific attachment site (att) of a host's chromosome.
78. A microorganism transformed with the plasmid of Claim 76.
79. The transformed microorganism of Claim 78 in which said plasmid replicates autonomously.
80. The polynucleotide according to Claim 71 wherein the hybrid PKS includes a chain-terminating thioesterase.
81. The polynucleotide of Claim 71 further comprising:  
(c) a third nucleic acid portion encoding at least one additional complete extension module of a Type I PKS.
82. The polynucleotide according to Claim 81 wherein the hybrid PKS includes a chain-terminating thioesterase.
83. The polynucleotide of Claim 81 wherein said third nucleic acid portion encodes a plurality of said complete extension modules.



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84. The polynucleotide according to Claim 83 wherein the hybrid PKS includes a chain-terminating thioesterase.
85. The polynucleotide according to Claim 71 wherein said loading module consists of an acyltransferase (AT) domain and an acyl carrier protein (ACP) domain.
86. The polynucleotide according to Claim 71, wherein said loading module utilizes a starter unit different from the starter unit utilized by said second Type I PKS.
87. The polynucleotide according to Claim 71, wherein said loading module is selected from the group consisting of: the loading module of the avermectin PKS of *Streptomyces avermitilis*, the loading module of the rapamycin PKS, the loading module of the FK506 PKS, and the loading module of the ascomycin PKS.
88. A nucleic acid comprising the polynucleotide of Claim 71 operably linked to a Type II PKS promoter.
89. The nucleic acid according to Claim 88 further comprising the natural activator gene for said promoter.
90. The nucleic acid according to Claim 88 wherein the Type II PKS promoter is the act I promoter of *S. coelicolor*.

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91. The nucleic acid according to Claim 90 further comprising the act II-orf4 natural activator gene for the act I promoter.
92. A method of producing a transformed microorganism comprising the steps of:
- (a) producing a plasmid which comprises donor DNA which comprises the polynucleotide of Claim 71, and
  - (b) transforming a microorganism with said plasmid, wherein said microorganism has a chromosome that includes DNA which undergoes homologous recombination with said plasmid to integrate said polynucleotide into the microorganism's chromosome.
93. A method of making a polyketide by culturing the microorganism of Claim 74 wherein said microorganism is an actinomycete selected from the group consisting of *Saccharopolyspora erythraea*, *Streptomyces coelicolor*, *Streptomyces avermitilis*, *Streptomyces griseofuscus*, *Streptomyces cinnamonensis*, *Micromonospora griseorubida*, *Streptomyces hygroscopicus*, *Streptomyces fradiae*, *Streptomyces longisporoflavus*, *Streptomyces lasaliensis*, *Streptomyces tsukubaensis*, *Streptomyces griseus*, *Streptomyces venezuelae*, *Streptomyces antibioticus*, *Streptomyces lividans*, *Streptomyces rimosus* and *Streptomyces albus*.

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94. A method of making a polyketide by culturing the microorganism of Claim 75 wherein said microorganism is an actinomycete selected from the group consisting of *Saccharopolyspora erythraea*, *Streptomyces coelicolor*, *Streptomyces avermitilis*, *Streptomyces griseofuscus*, *Streptomyces cinnamonensis*, *Micromonospora griseorubida*, *Streptomyces hygrosopicus*, *Streptomyces fradiae*, *Streptomyces longisporoflavus*, *Streptomyces lasaliensis*, *Streptomyces tsukubaensis*, *Streptomyces griseus*, *Streptomyces venezuelae*, *Streptomyces antibioticus*, *Streptomyces lividans*, *Streptomyces rimosus* and *Streptomyces albus*.

95. A method of making a polyketide comprising:

(a) transforming a host cells with the nucleic acid of Claim 90, and

(b) culturing said transformed host cell to effect synthesis of said polyketide;

wherein said host cells used in step (a) are selected from the group consisting of

*Saccharopolyspora erythraea*, *Streptomyces coelicolor*, *Streptomyces avermitilis*, *Streptomyces griseofuscus*, *Streptomyces cinnamonensis*, *Micromonospora griseorubida*, *Streptomyces hygrosopicus*, *Streptomyces fradiae*, *Streptomyces longisporoflavus*, *Streptomyces lasaliensis*, *Streptomyces tsukubaensis*, *Streptomyces griseus*, *Streptomyces venezuelae*, *Streptomyces antibioticus*, *Streptomyces lividans*, *Streptomyces rimosus* and *Streptomyces albus*.

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96. A method of making a polyketide comprising:

(a) transforming a host cells with the nucleic acid of Claim 91, and

(b) culturing said transformed host cell to effect synthesis of said polyketide;

wherein said host cells used in step (a) are selected from the group consisting of

*Saccharopolyspora erythraea*, *Streptomyces coelicolor*, *Streptomyces avermitilis*, *Streptomyces griseofuscus*, *Streptomyces cinnamonensis*, *Micromonospora griseorubida*, *Streptomyces hygrosopicus*, *Streptomyces fradiae*, *Streptomyces longisporoflavus*, *Streptomyces lasaliensis*, *Streptomyces tsukubaensis*, *Streptomyces griseus*, *Streptomyces venezuelae*, *Streptomyces antibioticus*, *Streptomyces lividans*, *Streptomyces rimosus* and *Streptomyces albus*.

97. The method of Claim 96 wherein said transformed host cell is *S. erythraea*.

98. A hybrid PKS encoded by the polynucleotide of Claim 71.---

*Reasons for Allowance*

23. The following is an examiner's statement of reasons for allowance. Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Allowed Claim 71 is representative of previously filed Claim 63 by Applicant. The specification and the prior art are replete with examples of polyketide synthase gene clusters whose general structure is described as follows (see also Figure 2)-

AT<sub>L</sub>-ACP<sub>L</sub>---KS<sub>E</sub>-AT<sub>E</sub>-ACP<sub>E</sub>---KS<sub>E</sub>-AT<sub>E</sub>-ACP<sub>E</sub>.....KS<sub>E</sub>-AT<sub>E</sub>-ACP<sub>E</sub>---KS<sub>E</sub>-AT<sub>E</sub>-ACP<sub>E</sub>.....etc.  
(L=loading module domain and E=extension module domain, one dash connecting domains, three dashes connecting modules on open reading frames and dots connecting open reading frames on the same gene cluster). The hybrid PKS claimed herein requires a combination of AT<sub>L</sub>-ACP<sub>L</sub>---KS<sub>E</sub> from one PKS and at least AT<sub>E</sub>-ACP<sub>E</sub> from another PKS wherein this extension module is "truncated" so as not to include the first KS domain. While the prior art teaches generic module and/or domain swapping of type I polyketide synthases, the *specific* hybrid, as noted above, is not anticipated and cannot be rendered obvious by the prior art.

Moreover, the scope of Claim 71 is **open** and encompasses not only a polynucleotide comprising the first open reading frame, but also nucleic acid sequence encoding additional extension modules and/or a thioesterase domain (see dependent Claims 80 and 81, for example) so that a "complete" PKS is encoded by the claims polynucleotide, which, at its most basic, contains a hybrid first open reading frame of the loading module and the first extension module.

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***Conclusion***

24. Claims 71-98 are allowed as amended above by the Examiner and as authorized by Applicant's representative.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (571) 272-0931. The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Kathleen M Kerr  
Primary Examiner  
Art Unit 1652

October 15, 2004